Pergamon

European Journal of Cancer Vol. 31A, No. 11, pp. 1790–1793, 1995

0959-8049/95 $9.50+0.00

0959-8049(95)00342-8

Original Paper

Disease Monitoring by the Tumour Markers Cyfra 21.1 and TPA in Patients with Non-small Cell Lung Cancer

A. van der Gaast, T.C. Kok, G.S. Kho, B.G. Blijenberg and T.A.W. Splinter

We evaluated the use of two tumour markers Cyfra 21.1 and tissue polypeptide antigen (TPA) for disease monitoring. Assessment of response to WHO criteria was compared to response assessment according to changes in the tumour marker levels. The criteria defined for marker response were a 65% decrease for a partial response and a 40% increase for progressive disease. When response evaluations with a positive lead time were included, 72% of 115 evaluations for Cyfra 21.1 and 59% of 107 evaluations for TPA yielded the same result. Most discordant evaluations were caused by those evaluations whereby the patient achieved a partial response according to the WHO criteria and had normalisation of the marker. Less cases with a positive lead time, more negative lead times, and more patients with progressive disease without an increase of the marker were seen with TPA compared to Cyfra 21.1. In conclusion, Cyfra 21.1 follows the changes in the tumour load better than TPA. Rising levels of both markers nearly always indicate disease progression, and such knowledge easily obtained may prevent the continuation of ineffective treatment.

Key words: non-small cell lung cancer, Cyfra 21.1, TPA
Eur J Cancer, Vol. 31A, No. 11, pp. 1790–1793, 1995

INTRODUCTION

MANY PATIENTS with non-small cell lung cancer (NSCLC) present with advanced disease or will relapse after initial surgery and/or radiotherapy, and may become candidates for systemic treatment. The impact of chemotherapy on survival is, however, small and the benefit seems to be restricted to those patients who achieve an objective response to treatment [1]. Therefore, monitoring of treatment and early detection of those patients who progress during treatment is important to avoid continuation of unnecessary toxic treatment.

The evaluation of response to chemotherapy may sometimes be difficult, especially in those cases where the bulk of disease is represented by non-evaluable lesions, and may require expensive and time-consuming investigations, such as computed tomography and magnetic resonance imaging.

In a recent study, we reported our first results with the tumour marker, Cyfra 21.1, the antibody to which detects a fragment of cytokeratin 19 in serum [2]. We showed that the sensitivity to Cyfra 21.1 in 212 patients with NSCLC, predominantly stage 3a-b and 4, was 40%. In addition, the sensitivity to another cytokeratin marker, tissue polypeptide antigen (TPA), tested in the same group of patients was also 40%. The sensitivities for both markers were higher in patients with stage 4 disease than in patients with stage 3 disease. Median levels of Cyfra 21.1 were significantly higher in patients with squamous cell carcinomas compared with the median levels found in patients with adenocarcinomas or large cell undifferentiated carcinomas. Furthermore, we demonstrated that Cyfra 21.1 was a useful marker for monitoring chemotherapy in patients with squamous cell carcinoma.

In the present study, we extended the monitoring data to include patients with adenocarcinoma and large cell undifferentiated carcinoma of the lung, and compared these results with those obtained with TPA. The TPA assay detects cytokeratins 8, 18 and 19 [3]. We have previously reported a high intermarker correlation between Cyfra 21.1 and TPA at diagnosis [2], and so investigated which one of these two markers would be the more accurate for disease monitoring.

PATIENTS AND METHODS

Patients

The initial cohort included 212 patients with histologically proven inoperable NSCLC, from whom serum samples were

Correspondence to A. van der Gaast.
A. van der Gaast, T.C. Kok and T.A.W. Splinter are at the Department of Medical Oncology; G.S. Kho is at the Department of Pulmonology; and B.G. Blijenberg and G.S. Kho are at the Department of Clinical Chemistry, University Hospital Rotterdam-Dijkzigt, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.
Revised 22 Mar. 1995; accepted 14 Jun. 1995.

collected at diagnosis and during treatment for those who received chemotherapy. From this group of patients, 50 fulfilled the following eligibility criteria: (1) treated with chemotherapy; (2) a sufficient number of marker determinations during chemotherapy i.e. at least three serum samples; (3) evaluable lesions; and (4) an elevated level of Cyfra 21.1 or TPA at the start of treatment.

All patients were staged according to the guidelines of the American Joint Committee on Cancer [4]. Nodal status was confirmed histologically or cytologically by mediastinoscopy, mediastinotomy or thoracotomy for those patients with stage IIIa disease. Response to chemotherapy was assessed, in general, after every two courses, according to standard WHO criteria [5] without knowledge of any tumour marker level. The following response criteria for tumour markers were used: complete response, normalisation of an elevated marker for at least 1 month; partial response, decrease of 65% or more of an elevated marker for at least 1 month; stable disease, less than 65% decrease or less than 40% increase of an elevated marker; progressive disease, more than 40% increase of an elevated marker level or a rise from below to above the cut-off level. These criteria are based on the assumption that the tumour marker levels correspond to three-dimensional measurements of the total body tumour load. A 50% decrease of a bidimensional measurement (WHO criteria) roughly corresponds to a 65% decrease of a volumetric measurement, and a 25% increase of a bidimensional measurement corresponds to a 40% increase of a volumetric measurement. When both methods of evaluation yielded the same result at the same time, the evaluation was called concordant.

Marker assessments

Serum Cyfra 21.1 assay values were determined using a solid-phase double determinant immunoradiometric assay (Centocor Diagnostics, Malvern, Pennsylvania, U.S.A.). This assay utilises two monoclonal antibodies (KS 19.1 and BM 19.21) reactive with different epitopes expressed by cytokeratin 19 fragments. KS 19.1 is coated on the solid phase and the BM 19.21 antibody, radiolabelled with iodine 125, is used as a tracer. For the Cyfra 21.1 assay, the coefficients for interassay variation were between 7.0 and 11.9%. TPA was measured with a commercial kit (Prolifigen RIA Sangtec Medical Co, Bromma, Sweden) according to the manufacturer's instructions.

Cut-off values used in this study were 3.3 ng/ml for Cyfra 21.1 and 170 U/l for TPA. These cut-off values correspond to a 96% specificity for both markers determined in 546 patients with non-malignant lung diseases [6].

Table 1. Patient characteristics

Characteristic	Number of patients (%) (n = 50)
No. patients with both markers elevated	37
No. patients with elevated TPA	41
No. patients with elevated Cyfra 21.1	46
Gender	
Female	10 (20%)
Male	40 (80%)
Median age (years)	58
Range	39–71
Performance (WHO)	
0	12 (24%)
1	32 (64%)
2	6 (12%)
Stage	
IIIa	13 (26%)
IIIb	11 (22%)
IV	26 (52%)
Histology	
Adenocarcinoma	12 (24%)
Squamous cell carcinoma	29 (58%)
Large cell undifferentiated	9 (18%)

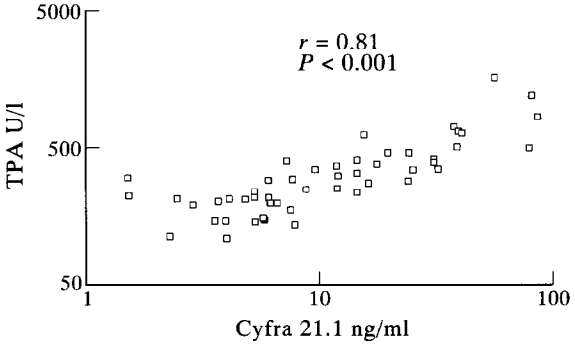

Figure 1. Scattergram of Cyfra 21.1 versus TPA.

RESULTS

The patient characteristics of the 50 eligible patients are listed in Table 1. 37 of the 50 patients had elevated levels of both Cyfra 21.1 and TPA.

A scattergram of the pretreatment levels of both markers is shown in Figure 1, demonstrating the high correlation between the two markers in pretreatment samples ($r = 0.81, P < 0.001$).

Disease monitoring with Cyfra 21.1

Of the 46 patients with an elevated Cyfra 21.1, 115 evaluations for response were performed. The concordance between the results of the clinical evaluations according to WHO criteria and the changes in the marker according to the earlier mentioned criteria was 63%.

Twenty-four of the 42 discordant evaluations were caused by patients with a clinical partial response and a decrease of the marker below the cut-off level (Table 2). Ten discordant evaluations could be explained by a positive lead time of the marker, i.e. the change in the tumour marker preceded the results obtained by the clinical evaluation by 1–2 months. On 9 of these 10 occasions, the marker indicated disease progression while the clinical response was stable disease; the tenth event occurred in a patient who had normalisation of the marker and stable disease, which later changed into a partial response. A negative lead time was observed once in a patient with progressive disease, while the tumour marker met the criteria for progressive disease only 4 weeks later. Five evaluations yielded stable disease clinically and a partial response according to the marker level on one occasion and a complete response indicated by the marker on four occasions. In most of these, tumour regression was observed, but was not sufficient to reach the

Table 2. Summary of discordant elevations of Cyfra 21.1

Total number of elevations	115
Number of discordant evaluations	42
Positive lead time	10
Negative lead time	1
Partial response according to WHO/complete response marker	24
Stable disease according to WHO/partial or complete response marker	5
Stable disease according to WHO/progressive disease marker	1
Progressive disease according to WHO/stable disease marker (marker increase less than 40%)	1

criteria for partial response. One patient had an increase in the marker level when clinical progression was documented, but this was not enough to meet the criteria set for marker progression. The last discordant evaluation was in a patient who had progressive disease according to the marker, but stable disease according to the WHO criteria. This patient was subsequently treated with radiotherapy so that the possibility of a positive lead time of the marker could not be assessed. A summary of the discordant evaluations of Cyfra 21.1 is given in Table 2.

Disease monitoring with TPA

Of 41 patients with an elevated TPA, 107 evaluations for response were performed. The concordance between the results of the clinical evaluations according to WHO criteria and the changes in the marker was 54%.

Five of the 49 discordant evaluations were due to a positive lead time of the marker, whereby the marker indicated disease progression while the clinical response was stable disease (Table 3). A negative lead time was seen four times in patients with clinical progressive disease and progressive disease according to the tumour marker criteria 1–2 months later. In 5 patients with disease progression according to the WHO criteria, the marker levels remained stable. A reduction in the TPA levels below the cut-off level was seen on 23 occasions when the clinical response was a partial response and on 11 occasions when the clinical response was stable disease. In one patient with a partial response, the marker level indicated stable disease. A summary of the discordant evaluations of TPA is given in Table 3.

In Figure 2, an example is shown of Cyfra 21.1 and TPA levels during treatment, whereby the course of both markers is identical. An example of a patient with progressive disease and increasing Cyfra 21.1 levels, but a stable level of TPA is shown in Figure 3.

Table 3. Summary of discordant evaluations of TPA

Total number of evaluations	107
Number of discordant evaluations	49
Positive lead time	5
Negative lead time	4
Partial response according to WHO/complete response marker	23
Stable disease according to WHO/partial or complete response marker	11
Progressive disease according to WHO/stable disease marker	5
Partial response according to WHO/stable disease marker	1

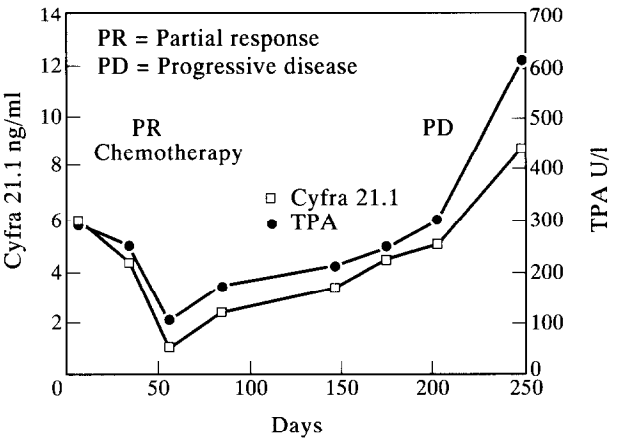

Figure 2. Course of Cyfra 21.1 and TPA during chemotherapy in a patient with a stage 4 adenocarcinoma of the lung.

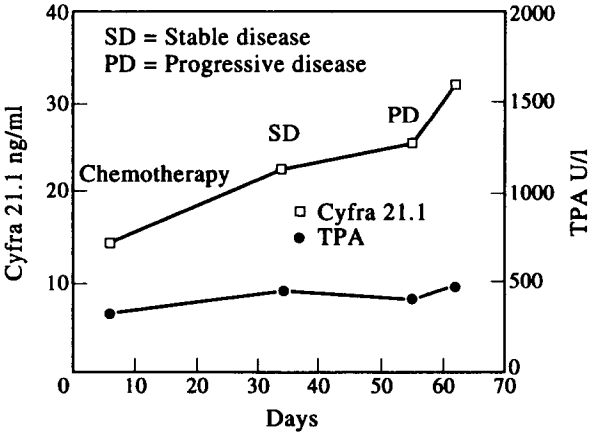

Figure 3. Course of Cyfra 21.1 and TPA during chemotherapy in a patient with a stage 4 squamous cell carcinoma of the lung.

DISCUSSION

The most common application of serum tumour markers is disease monitoring, and tumour markers such as alpha-fetoprotein, β-chorionic gonadotropin, prostate specific antigen, CA-15.3 and C-125 have become invaluable in the management of patients with testicular, prostate, breast and ovarian cancer [7].

The aim of the present study was to investigate whether Cyfra 21.1 and TPA are useful serum tumour markers for disease monitoring in patients with NSCLC during chemotherapy.

Although a number of studies have investigated the role of TPA for disease monitoring in NSCLC patients, in virtually none have criteria been defined for marker response nor been correlated with response assessments according to standard WHO criteria. Monitoring data for Cyfra 21.1 are scarce. Since both markers measure cytokeratins, cytokeratin 19 for Cyfra 21.1 and cytokeratin 8, 18 and 19 for TPA, we were also interested in a comparison between these two markers. Moreover, it has also been claimed that the serum levels of TPA are indicative of the proliferation activity of a tumour [8].

Using strictly defined criteria for a marker response (i.e. a 40% increase of the marker level for disease progression and a 65% decrease in the marker level for a partial response) and considering evaluations with a positive lead time as concordant, we found a concordance between response evaluation according

to standard WHO criteria and response evaluation according to the marker criteria of 72% and 59% for Cyfra 21.1 and TPA, respectively. A substantial number of discordant evaluations for both markers were caused by those evaluations whereby the patient achieved only a partial response according to the WHO criteria and had a decrease of the marker level below the cut-off level. Although such evaluations are discordant, they usually do not influence the treatment strategy for these patients.

The differences between the two markers were that a positive lead time, whereby the marker indicated disease progression earlier than the evaluation according to the WHO criteria, was observed on nine occasions for Cyfra 21.1 and on five occasions for TPA. Furthermore, on nine occasions in patients with progressive disease, TPA levels increased only marginally or remained stable or met the criteria for marker response 1 month later. A third difference between TPA and Cyfra 21.1 was that more patients with stable disease had normalisation of the TPA levels compared with Cyfra 21.1. It thus seems that in some patients with progressive disease TPA is less well correlated with increase in tumour load than Cyfra 21.1, and further that more patients with stable disease have decreasing levels of TPA below the cut-off level than is observed with Cyfra 21.1. Whether these two observations are due to the fact that TPA levels may be correlated with the proliferation rate of the tumour rather than the total tumour load remains obscure. We were not able to find a relationship between the height of the serum levels of TPA and the best WHO response to treatment (data not shown).

In conclusion, using strictly defined criteria for tumour marker response, Cyfra 21.1 follows the changes in the tumour load, which are still the basis for clinical decisions concerning continuation of treatment, better than TPA. Rising levels of both markers during chemotherapy nearly always indicate disease progression, and such information may prevent the continuation of ineffective treatment. The precise relationship between TPA and proliferation and the therapeutic implications, if any, remains unclear.

1. Souquet PJ, Chauvin F, Boissel JP, *et al.* Polychemotherapy in advanced non small cell lung cancer: a meta-analysis. *Lancet* 1993, **342**, 19–21.
2. Gaast A van der, Schoenmakers CHH, Kok TC, Blijenberg BG, Cornillie F, Splinter TAW. Evaluation of a new tumor marker in patients with non-small cell lung cancer: Cyfra 21.1. *Br J Cancer* 1994, **69**, 525–528.
3. Hansson LO. Comparison of two assays (TPA and TPS) for cytokeratin polypeptides in serum using three different patient groups and in healthy subjects. In Klapdor R, ed. *Current Tumour Diagnosis: Applications, Clinical Relevance, Research Trends.* Munchen, W Zuckschwerdt, 1993, 28.
4. American Joint Committee on Cancer. In Beahrs OH, Henson DE, Hutter RV, Myers MH, eds. *Manual for Staging of Cancer.* Philadelphia, J.B. Lippincott, 1988, 115–122.
5. WHO. *Handbook of Reporting Results of Cancer Treatment.* Geneva, World Health Organization Offset publication No. 48, 1979.
6. Rastel D, Ramaioli A, Cornillie F, Thirion B. Cyfra 21.1, a sensitive and specific new tumour marker for squamous cell lung cancer. Report of the first European multicentre evaluation. *Eur J Cancer* 1994, **30**, 601–606.
7. Bates SE. Clinical applications of serum tumor markers. *Intern Med* 1991, **115**, 623–638.
8. Bjorklund B, Bjorklund V. Biochemische und morphologische grundlagen von TPA. In Luthgens M, Schegel G, eds. *Tumormarkersystem CEA-TPA.* Leonberg, Tumor Diagnositik, 1987, 14–30.

Acknowledgement—Supported by a grant from Centocor Diagnostics, Leuven, Belgium.